Discovery, invention, and innovation: Are they really different?

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Introduction

Discovery, invention, and innovation are usually regarded as different concepts. In general, a discovery is defined as something that already existed but had not been found, while an invention is a new product or process that solves a technical problem (World Intellectual Property Organization, 2007). And, innovation is commonly known as the commercialization of invention.

Different from those holding mainstream views, Lane and Flagg (2010) underlined that discovery, invention, and innovation are of the same nature, which is knowledge, but of different states, analogous to the three distinct physical forms of matter: gas (discovery), liquid (invention), and solid (innovation). According to Lane and Flagg, generation of a technological solution to a specific problem may require creation of knowledge in a step-by-step manner (**Fig. 1**). At first, a knowledge gap is identified and filled by research activity which discovers novel knowledge, called "discovery". Discovery state of knowledge is intangible and highly malleable as it is merely conceptual and can be revised, rejected, or dispersed. Therefore, knowledge at discovery stage is analogous to matter at gas phase (**Fig. 1**). Subsequent development activity transforms discovery to an invention, a proof-of-concept prototype that demonstrates the feasibility of the discovery. Compared to the discovery state of knowledge, invention is moderately tangible yet still malleable that it may be shaped in different ways. As such, knowledge at invention stage is equivalent to matter at liquid phase (**Fig. 1**). Finally,

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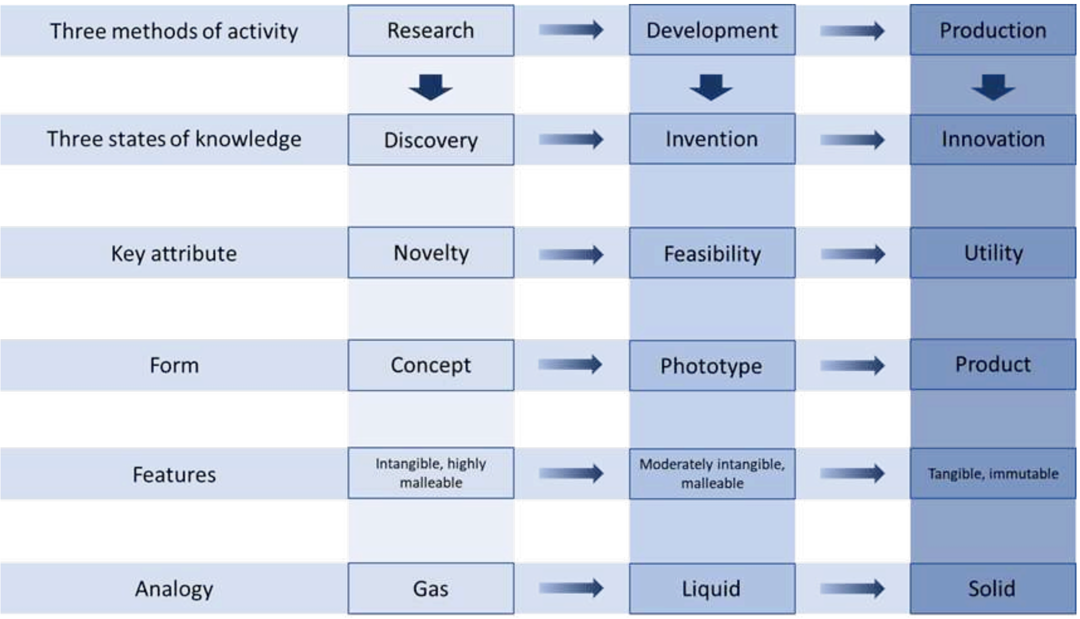
production activity further refines the invention leading to the final form of knowledge: innovation (product, device or service) which possesses utility. However, innovation is locked in its final version that further modification is no longer allowed due to high level of specification. Hence, knowledge at innovation stage is analogous to matter at solid phase as it is tangible and immutable (**Fig. 1**).



Three methods of activity	Research	Development	Production
Three states of knowledge	Discovery	Invention	Innovation
Key attribute	Novelty	Feasibility	Utility
Form	Concept	Phototype	Product
Features	Intangible, highly malleable	Moderately intangible, malleable	Tangible, immutable
Analogy	Gas	Liquid	Solid

Fig. 1 Schematic illustration of discovery, invention, and innovation based on Lane and Flagg's paper (2010) entitled "translating three states of knowledge-discovery, invention, and innovation".

Indeed, in many cases, a specific problem is solved by a technology-based solution resulting from sequential transformations of different states of knowledge: discovery, then invention, and eventually innovation. This classical pathway of knowledge progression is analogous to the transits of phase of matter from gas (discovery) to liquid (invention) through condensation, and then from liquid (invention) to solid (innovation) through solidification. In fact, in addition to condensation and solidification, other forms of transitions also exist, including transformations from liquid (invention) to gas (discovery) by evaporation, from solid (innovation) to liquid (invention) by melting, from solid (innovation) to gas (discovery) by sublimation, and from gas (discovery) to solid (innovation) by deposition (**Fig. 2**). These reversible processes are supported by examples in the field of molecular biotechnology and biomedical science, which are provided in the next sections.

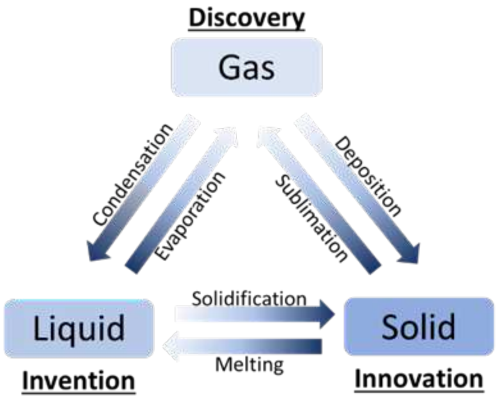


Fig. 2 Schematic illustration of the transformations between discovery, invention, and innovation, analogous to the transitions between gas, liquid, and solid.

Invention and reinvention of polymerase chain reaction (PCR) technique

Polymerase chain reaction (PCR) is a molecular biology technique initially invented by Kary Mullis (Mullis K, Faloona F, Scharf S, Saiki R, Horn G, & Erlich H, 1986). This technology revolutionized biological research as it allows scientists to amplify a trace quantity of specific DNA template in a sample to a large amount for detection and/or production purpose. The procedure of a PCR cycle is composed of three steps controlled by variation in temperature: (1) denaturation of double stranded DNA template into single strands (at 95°C); (2) annealing of specific primers to each strand of the template DNA (at 50-65°C); and (3) elongation of new DNA strands from the primers by DNA polymerase (at 72°C) (Lorenz TC, 2012). Each cycle of reaction doubles the DNA template of interest, eventually resulting in several millions of copies after 20-40 cycles of synthesis. The automation of PCR was achieved by the invention and innovation of thermal cycler (Zhu H, Zhang H, Xu Y, Laššáková S, Korabečná M, & Neužil P, 2020), which allows controlled and progressive chain reaction.

Although the principle of PCR is quite straightforward and simple, it is based on the great discoveries of DNA double helix (Watson JD, & Crick FH, 1953), mechanism of DNA replication (Werner R, 1971; KleppeK, Ohtsuka E, Kleppe R, Molineux I, & Khorana HG, 1971), and thermostable DNA polymerase (Chien A, Edgar DB, & Trela JM, 1976) (**Fig. 3**). Upon first commercialization of PCR in 1987, the development efforts in strengthening the function of PCR continued, leading to the inventions of quantitative real-time PCR (qPCR)

(Higuchi R, Fockler C, Dollinger G, & Watson R, 1993) and digital PCR (dPCR) (Vogelstein B, & Kinzler KW, 1999) (**Fig. 3**). While the conventional PCR technique merely allows semi-quantification of specific DNA from a sample, qPCR and dPCR enable quantification of template DNA with significantly higher accuracy. dPCR even allows absolute quantification of the initial templates. The key modifications that distinguish qPCR and dPCR from the conventional PCR include the introduction of fluorescence-based detection system and the partition of reaction, respectively. However, although qPCR and dPCR allow improved detection of target DNA in terms of accuracy, they are no longer appropriate for the production purpose due to the modifications. Therefore, conventional PCR is not replaced by, but coexists with qPCR and dPCR on the market as they serve different purposes (conventional PCR: semi-quantitative detection of specific DNA from a sample, and productive amplification of specific DNA from a sample; qPCR: quantitative detection of specific DNA from a sample; dPCR: absolutely quantitative detection of specific DNA from a sample).

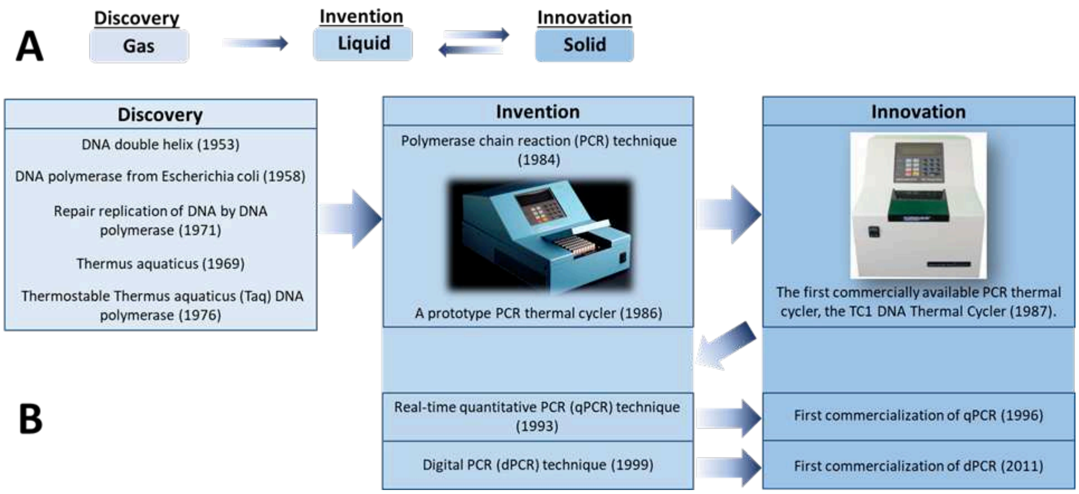

A
Discovery
Gas
Invention
Liquid
Innovation
Solid
Discovery
DNA double helix (1953)
DNA polymerase from Escherichia coli (1958)
Repair replication of DNA by DNA polymerase (1971)
Thermus aquaticus (1969)
Thermostable Thermus aquaticus (Taq) DNA polymerase (1976)
Invention
Polymerase chain reaction (PCR) technique (1984)
A prototype PCR thermal cycler (1986)
Innovation
The first commercially available PCR thermal cycler, the TC1 DNA Thermal Cycler (1987).
B
Real-time quantitative PCR (qPCR) technique (1993)
Digital PCR (dPCR) technique (1999)
First commercialization of qPCR (1996)
First commercialization of dPCR (2011)

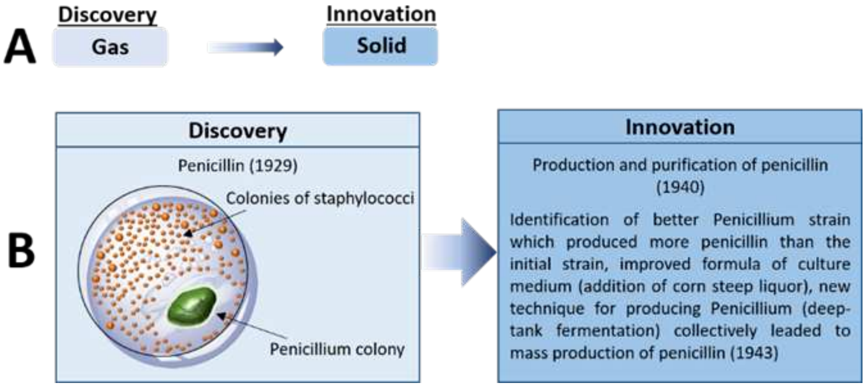
Fig. 3 Schematic illustration of the invention and reinvention of polymerase chain reaction (PCR) technique. (A) State transformations of PCR knowledge analogous to the phase transitions of matter. (B) State transformations of PCR knowledge. The photo of the prototype PCR thermal cycler is referenced from the website of Science Museum Group. The photo of the first commercially available PCR thermal cycler is referenced from the website of Thermo Fisher Scientific.

Discovery of penicillin

Penicillin, the first antibiotic agent in the history, since being discovered by Alexander Fleming (Fleming A, 1929), has saved millions of lives and changed the course of history. In addition, it laid the foundations of the era of antibiotics and stimulated the subsequent development of other antibiotics with more potency (Lobanovska M & Pilla G, 2017).

> "I did not invent penicillin. Nature did that. I only discovered it by accident."

As said by Fleming himself (Tan SY & Tatsumura Y, 2015), penicillin was discovered rather than invented. In 1928, after returning to his laboratory from vacation, Fleming noticed that one of his cell-culture dishes containing staphylococci was contaminated (Swann JP, 1983) (**Fig. 4**). Subsequent observation revealed that the growth of bacteria in dish was inhibited by fungal contaminant, which was later turned out to be Penicillium notatum, and the antibacterial substance it produced was referred to as penicillin (Fleming A, 1929). Since 1939, during World War II, British scientists Howard Florey, Ernst Chain, Norman Heatley and their colleagues designed methods for and achieved isolation and purification of penicillin in large quantities (Tan SY & Tatsumura Y, 2015) (**Fig. 4**). Moreover, they conducted animal and clinical tests which provided key evidences that penicillin is a life-saving drug (Chain E, Florey HW, Gardner NG, Heatley NG, Jennings MA, Orr-Ewing J, et al. 1940; Ligon BL, 2004; Lobanovska M & Pilla G, 2017). Although this British team devised methods for the mass production of penicillin, it was not achieved in the United Kingdom due to the unavailability of resources during war. Therefore, in 1941, Florey and Heatley traveled to the United States (US) to seek support (Lobanovska M & Pilla G, 2017). In the US, further innovations were made in increasing the yield of penicillin, these include: (1) identification of better Penicillium strain which produced more penicillin than Fleming's initial strain; (2) the formula of culture medium was improved by the addition of corn steep liquor; (3) deep-tank fermentation, a new technique for producing Penicillium was introduced (**Fig. 4**). These innovations collectively lead to mass production of penicillin (Gaynes R, 2017). In 1943, sufficient production of penicillin successfully fulfilled the demands of the Allied Armed Forces (American Chemical Society, 1999).



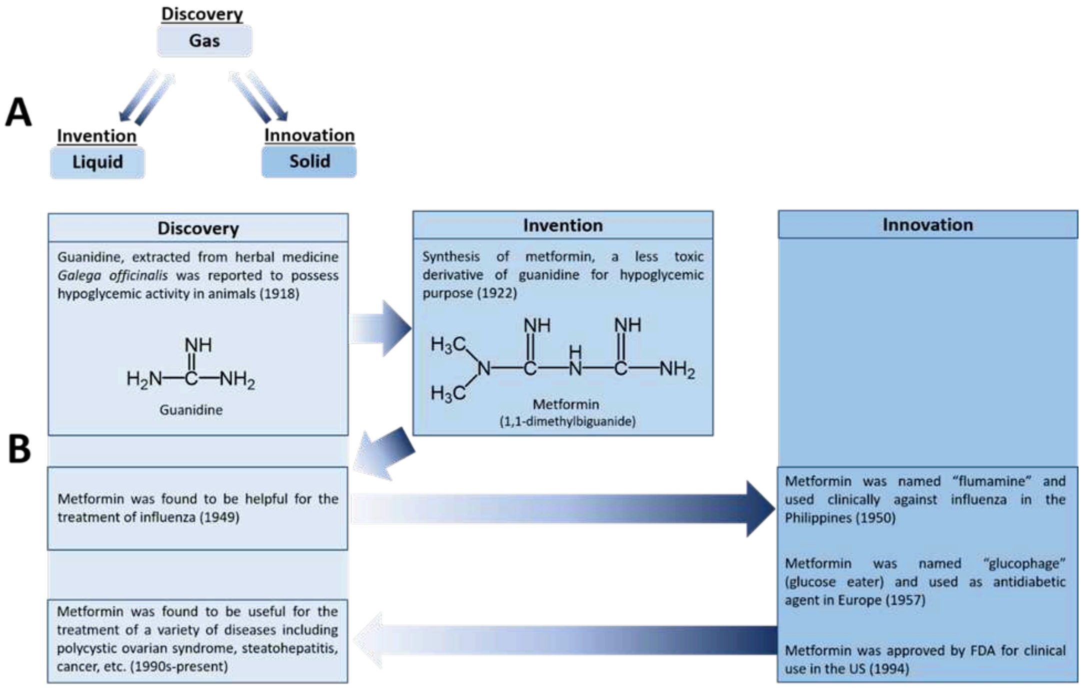
Identification of better Penicillium strain which produced more penicillin than the initial strain, improved formula of culture medium (addition of corn steep liquor), new technique for producing Penicillium (deep-tank fermentation) collectively leaded to mass production of penicillin (1943)

Fig. 4 Schematic illustration of the discovery of penicillin. (A) State transformation of penicillin knowledge analogous to the phase transition of matter. (B) State transformation of penicillin knowledge.

Discovery and rediscovery of metformin

Metformin is a first-line oral hypoglycemic agent for the treatment of diabetes. Its invention was based on the discovery that guanidine, a bioactive compound found in herbal medicine *Galega officinalis*, could reduce blood glucose level in animals (Watanabe CK, 1918) (**Fig. 5**). As guanidine was too toxic for use, a number of its derivatives, either naturally occurring or synthesized, were subsequently prepared and tested for their hypoglycemic activities in the 1920s (Bailey CJ, 2017). These guanidine derivatives include galegine (extracted from *Galega officinalis*), synthalin A, synthalin B, proguanil, buformin, phenformin, and metformin. Galegine and synthalin A/B were used clinically in the 1920s but later discontinued due to their toxicity and limited efficacy. Metformin, first synthesized in 1922 (Werner EA & Bell J, 1922) (**Fig. 5**), was reported to showed the least toxicity compared to other guanidine derivatives (Slotta KH & Tschesche R, 1929). However, due to the high doses required for exerting a hypoglycemic effect in animals, the real potential of metformin as an antidiabetic agent was underappreciated at the time (Bailey CJ, 2017). Instead, metformin was tested for its antimalarial activity in 1940s, yet leading to the surprised discovery of its utility in combating influenza (**Fig. 5**). As a result, metformin was called "flumanime" and used clinically in the Philippines as an anti-influenza drug in 1949 (Garcia EY, 1950) (**Fig. 5**).

In the 1950s, Jean Sterne conducted the study of metformin in humans which provided sufficient evidence on its satisfactory glucose-lowering efficacy and safety profile in diabetic patients (Sterne J, 1957). Metformin was then named “glucophage”, meaning glucose eater in French, and introduced as an antidiabetic medicine in Europe (Pasik C, 1997) (**Fig. 5**). Metformin eventually entered the US market on 1994 (Howlett HCS & Bailey CJ, 2007). Since 1990s, rediscoveries on the therapeutic potential of metformin have been accumulating and updating, making this compound a versatile drug. So far, clinical or investigational use of metformin has been expanded to the treatment of polycystic ovarian syndrome, steatohepatitis, HIV-related metabolic abnormalities, and cancers (Hajjar J, Habra MA & Naing A, 2013) (**Fig. 5**).



Guanidine, extracted from herbal medicine *Galega officinalis* was reported to possess hypoglycemic activity in animals (1918)

Synthesis of metformin, a less toxic derivative of guanidine for hypoglycemic purpose (1922)

Metformin was found to be helpful for the treatment of influenza (1949)

Metformin was found to be useful for the treatment of a variety of diseases including polycystic ovarian syndrome, steatohepatitis, cancer, etc. (1990s-present)

Metformin was named “flumamine” and used clinically against influenza in the Philippines (1950)

Metformin was named “glucophage” (glucose eater) and used as antidiabetic agent in Europe (1957)

Metformin was approved by FDA for clinical use in the US (1994)

Fig. 5 Schematic illustration of the discovery and rediscovery of metformin. (A) State transformations of metformin knowledge analogous to the phase transitions of matter. (B) State transformations of metformin knowledge.

Conclusion

Discovery, invention, and innovation are homogeneous knowledge in nature. This is supported by the fact that reversible transformations between any two states of knowledge can occur, which is analogous to the transitions between different phases of matter(**Fig. 2**). Therefore, contrary thinking (reverse brainstorming) and non-linear thinking are very helpful in generating new knowledge. It is wished that this paper will encourage creativity of readers across disciplines and backgrounds, particularly from the field of biotechnology.

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